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Original Article

Difficult morning awakening from rapid eye movement sleep and impaired cognitive function in delayed sleep phase disorder patients

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ABSTRACT

Objectives: Difficult awakening is a key symptom of delayed sleep phase disorder (DSPD), but no studies have quantified awakening thresholds in a sleep laboratory. This study assessed whether cognitive function was impaired after awakening and whether difficult awakening was associated with specific polysomnographic features such as slow wave sleep stage N3.
Methods: Nine patients with DSPD and nine sex- and age-matched healthy controls were included. Polysomnography was performed at our university hospital from midnight. An alarm clock was activated at 07:00 with sound intensity increasing from 72 to 104 dB. Participants performed a continuous performance test (CPT) the previous afternoon and immediately upon awakening.
Results: Three DSPD patients and zero controls did not wake up to the maximum 104 dB alarm sound; all three patients were in rapid eye movement (REM) sleep when the alarm clock went off (difference in proportions, $P = 0.047$). In patients, CPT reaction time was prolonged in the morning compared to the afternoon [analysis of variance (ANOVA) interaction, $P = 0.01$]. DSPD patients made more omission errors than controls regardless of time of the day (ANOVA main effect, $P = 0.046$).
Conclusion: Difficult awakening from slow wave sleep was not observed. A subgroup of DSPD patients may have a severe problem waking up from REM sleep. DSPD patients may also have a state-like impairment in cognitive function in the morning and a trait-like impairment not depending on time of day, compared to normal sleepers.

1. Introduction

Delayed sleep phase disorder (DSPD) prevalence among high school students may be as high as 8.4% [1], whereas the prevalence in adults may be as low as 0.17% [2].

Some patients with DSPD report extreme difficulty with waking up in the morning, as they do not react to an alarm clock [3]. Patients may be unable to keep a job or have problems completing education because of absence in the morning [4,5].

Whereas difficult morning awakening is a diagnostic criterion (ICSD-2) and highly disabling symptom in DSPD, research on this phenomenon has not yet been conducted [3]. Specifically, it has not been tested whether patients have a different wake-up threshold compared to healthy controls in the morning. Moreover, no studies have explored potential mechanisms for why these patients have difficulties waking up. Most awakenings in healthy subjects follow a rapid eye movement (REM) sleep period [3,5,6]. On the other hand, awakening from slow wave sleep (SWS) may be difficult, often resulting in confusion and impaired arousal [7]. The difficult morning awakening for patients with DSPD could therefore be related to sleep stage [8].

DSPD patients commonly report poor cognitive function when forced to arise early in the morning. Temporarily impaired cognitive function upon awakening is also a characteristic of sleep inertia (SI) [7,9], and its severity has been related to awakening during slow wave sleep (N3) and after reduced total sleep time (TST) [7,10]. Consequently as DSPD patients have considerable amounts of N3 sleep between 06:00 and 08:00 [8], it may be hypothesized that difficult awakening mainly occurs from N3 in patients with DSPD.

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It has been suggested that SI is primarily associated with low arousal (increased reaction time), whereas SI in the context of sleep deprivation also introduces lapses in vigilance (reduced accuracy) [11]. The continuous performance test (CPT) has the capacity to reliably assess both speed and accuracy [12,13], and measures both sustained and transient cognitive control processes that are subserved by brain regions [14] shown to be particularly prone to SI effects [15].

One aim was to quantify the awakening threshold in DSPD patients with an alarm clock. Another hypothesis was that cognitive function would be reduced upon awakening relative to daytime performance in DSPD patients compared to healthy controls. A third hypothesis was that difficult awakenings would be associated with some sleep stage (SWS in particular).

2. Methods

2.1. Participants

Patients were interviewed by physicians experienced with sleep disorders using a semi-structured interview. Nine patients diagnosed with DSPD were included in the study (four males, five females) (mean age, 22.5 ± 2.2 years; range, 18–25). The included patients met the Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV 307.45) diagnostic criteria for circadian rhythm sleep disorder [16] and the ICSD-2 criteria for DSPD [17].

Nine healthy subjects (four males and five females) (mean age 23.3 ± 2.4 years; range, 18–28) were recruited by posting an announcement on the University's homepage and local campus boards.

Subjects with coexisting other major health problems or regular use of neuroactive drugs the last 4 weeks were not included.

The study protocol was approved by the Regional Committee for Medical and Health Research Ethics.

2.2. Procedure

Participants completed a sleep diary for 14 days and wore an actigraph for the last 7 days before polysomnography (PSG) was recorded for two nights. An ambulatory PSG was done first to minimize the 'first-night effect' [18].

The experimental PSG was performed two days after the initial PSG. Participants came to the sleep laboratory at 14:00, took the CPT at 15:00, and completed psychiatric and sleep-related questionnaires afterwards. The light was dimmed to <200 lux from 18:00. Saliva was sampled for melatonin testing every hour from 19:00 to bedtime at midnight. At exactly 07:00 the following morning, an alarm clock was activated. This custom-made tone generator started at 72 dB sound pressure level, increasing by 2 dB at equal intervals (sound active for 4.4 s with 5 s intervals) until the subject was awake or the 104 dB maximum was reached after 3 min. Two standard personal computer speakers (Sony, SRS-Z510) were placed on each side, ~50 cm from the head. The exact time and dB value at which each person reacted were noted. Subjects who did not react at all to 104 dB alarms were awakened manually. Six minutes after awakening the participants took the same CPT test, with identical instructions as the day before.

2.3. Assessments

2.3.1. Actigraphy

The actigraph (AW4, CamNtech Ltd, Cambridge, UK) recorded 30 s epochs for 7 days prior to the experimental night with medium sensitivity. We used sleep start and sleep end for analyses.

2.3.2. Polysomnography

Participants slept in a standard hospital bed within a shielded video-PSG laboratory. A Somnoscreen 10-20 monitor (SOMNOmedics GmbH, Randersacker, Germany) using a standard PSG montage with electroencephalography electrodes (F3, F4, C3, C4, O1, O2, A1, A2 with a Cz reference, and 0.2–35 Hz filter), electro-oculography electrodes (placed 1 cm over/under the left/right lateral canthus), an infrared O_2 finger sensor, two chin EMG electrodes, a nasal airflow sensor and an oro-nasal thermistor were used. Apnea-hypopnea index was <5/h in all participants. Video and sound were recorded continuously (VID65A, HD resolution 2048 × 1536, SOMNOmedics). Polysomnograms were analyzed by a blinded, certified clinical neurophysiologist, according to standardized criteria [19] using Domino software version 2.5.0.

2.3.3. Melatonin

Food or drink was not allowed 30 min prior to each sampling. Five minutes before sampling, the mouth was rinsed with cold water. A piece of Parafilm® (Pechiney Plastic Packaging Company, Chicago, IL, USA) was chewed and two samples of ≥2 mL each were collected and placed in a refrigerator at 4 °C within 10 min. All samples were placed in a freezer at less than –20 °C immediately after midnight and analyzed with the Non-Extraction Melatonin Saliva enzyme-linked immunosorbent assay kit, supplied by IBL International GmbH (Hamburg, Germany).

A melatonin baseline was calculated as the mean value for samples taken at 20:00, 21:00 and 22:00. Normal (early) melatonin secretion onset was defined when a concentration either more than twice the baseline value, or baseline +2.5 standard deviations (SD), was measured either at 23:00 or at 00:00. This cut-off was modified from the 2 SD limit used by Chang et al. [20] in order to account for the observed baseline variability. Delayed dim light melatonin onset (DLMO) was presumed if concentrations had not reached one of the cut-off values at 00:00.

2.3.4. Sleep diary

Participants kept a graphic sleep diary of their subjective experience of sleep timing and duration for 14 days prior to the experimental night. A pencil was used to shade (or leave) 24 rectangular small boxes each representing 1 h of the day. Symbols were inserted for going to bed, lights off, and getting out of bed.

2.3.5. Sleep-related and psychiatric self-report questionnaires

Participants completed self-report questionnaires to assess circadian preference (Horne–Östberg Morningness Eveningness Questionnaire (MEQ) [21], and the Beck Depression Inventory (BDI) [22]).

2.3.6. Continuous performance test

In the present study, Conners' CPT II [23] was used to assess cognitive function. Letters A–Z were presented consecutively on a computer screen for 250 ms each in a pseudorandom fashion for 14 min. Inter-stimulus intervals varied between 1, 2 and 4 s. There were 324 targets (letters other than X) and 36 non-targets (the letter X). Participants were instructed to press a button as quickly as possible whenever a target was presented. Measures were: Hit-RT, mean reaction time for correct responses; commission errors, the number of failed withholdings to non-targets; and omission errors, the number of failed responses to targets.

2.4. Data analysis and statistics

The main variables were: CPT Hit-RT evening–morning difference; alarm clock level upon awakening; and sleep stage on awakening. Exploratory statistical data analysis was performed for the remaining variables.

The value of 105 dB was entered for subjects who did not wake up to 104 dB, whereas a value of 71 dB was entered for subjects who were awake at 07:00.

Separate 2 × 2 repeated measures analysis of variance (ANOVA) was applied for each of the three CPT performance measures (Hit-RT, commission errors, omission errors), with group (patients, controls) and time (afternoon, morning) as fixed factors. In the case of statistically significant main or interaction effects, planned simple contrasts were performed.

Non-parametric Mann–Whitney *U*-test or Wilcoxon signed rank test was applied for PSG, actigraphy, questionnaire, and sleep diary variables. Differences in proportions were tested with a standardized normal deviate. Two-sided $P < 0.05$ was considered significant.

Non-parametric Spearman's rho was used for exploratory correlation analyses within the patient group.

3. Results

Delayed DLMO was confirmed in eight out of the nine patients. Melatonin increased significantly more in controls than in patients (Table 1).

Self-reported MEQ, sleep diary and actigraphy data confirmed a delayed sleep phase in all patients. Patients scored higher on depression than did controls. Based on standard BDI cut-off values (0–9, normal; 10–18, mild; 19–29, moderate; ≥30, severe depression), all controls were normal. Three patients were normal, four mild, and two had severe depression. No significant difference was found regarding diary-reported sleep duration between the two groups (Table 1).

PSG sleep onset latency was longer, total sleep time (TST) was shorter, sleep efficiency (SE) was lower and stage N3 duration was shorter in patients compared to healthy controls (Table 2).

Patients tended to be more difficult to wake up, as quantified through the intensity of the alarm clock sound, but the variation was larger within the patient group and the difference was not significant (Table 2).

Compared to none of the nine controls, three of nine patients failed to wake up from the alarm clock at its highest intensity (104 dB) and had to be manually awakened. All patients who failed to wake up from the alarm clock were in REM sleep at the time of the alarm.

Four patients and three controls were in REM sleep at the time of the alarm. Three out of these four patients compared to none of three controls did not wake up from REM sleep ($P = 0.047$). Patients who failed to wake up from REM ($n = 3$) had significantly less REM percentage (14 ± 5 vs 19 ± 2%, $P = 0.04$) and more stage N1 sleep (35 ± 9 vs 17 ± 12 min, $P = 0.04$) than the other patients ($n = 6$), whereas no significant differences were observed for melatonin (baseline and percent increase) and diary-recorded variables (sleep length, sleep latency, sleep onset hour, and sleep onset hour variability).

CPT performance measures are presented in Table 3. For Hit-RT, there was a statistically significant interaction effect between group and time [$F(1, 16) = 7.76$, $P = 0.013$] (Fig. 1). A planned simple contrast revealed that patients had a statistically significant

Table 1
Sleep diary, actigraphy questionnaire and melatonin data.

Variables	Patients ($n = 9$)	Controls ($n = 9$)	*P*-value[a]
Sleep diary			
Sleep start	01:26 ± 01:03	00:03 ± 00:41	0.004
Sleep end	10:23 ± 01:03	07:55 ± 00:53	<0.0005
Night sleep (h)	7.44 ± 0.69	7.14 ± 0.41	NS
Actigraphy			
Sleep start	01:48 ± 00:47	00:23 ± 00:46	0.003
Sleep end	09:50 ± 1:26	08:05 ± 00:56	0.02
Questionnaires			
BDI	14.7 ± 11.7	2.8 ± 2.9	0.01
MEQ	27.6 ± 6.0	46.8 ± 6.4	<0.0005
Melatonin			
Baseline (pg/mL)	11.0 ± 6.3	9.3 ± 5.7	NS
Percent increase[b]	37 ± 51	137 ± 109	0.01
Delayed DLMO (no.)	8	3	0.02

Values are mean ± standard deviation unless otherwise indicated.
BDI, Beck Depression Inventory; MEQ, Morningness–Eveningness Questionnaire; DLMO, dim light melatonin onset; NS, not significant.
[a] Mann–Whitney *U*- or proportion-difference test.
[b] Maximum increase at 23:00 or 00:00.

Table 2
Polysomnographic data and awakening threshold for the study night recorded from 00:00 to 07:00.

Sleep variable	Patient	Control	*P*-value[a]
TST (min)	333 ± 49	379 ± 22	0.01
SE (%)	82.5 ± 10.7	93.3 ± 5.4	0.01
SOL (min)	41 ± 37	7 ± 7	0.003
N1 (min)	30 ± 13	43 ± 43	NS
N2 (min)	178 ± 31	156 ± 26	NS
N3 (min)	73 ± 16	106 ± 27	0.01
REM (min)	53 ± 19	74 ± 21	NS
Awakening threshold (dB)	85.2 ± 14.9	74.2 ± 2.7	NS

Values are mean ± standard deviation.
TST, total sleep time; SE, sleep efficiency; SOL, sleep onset latency to N1; REM, rapid eye movement sleep; NS, not significant.
[a] Mann–Whitney *U*-test.

Table 3
Summary of CPT measures.

CPT measure	Afternoon (~15:00)	Morning (07:00)
Hit RT (ms)		
Patients	300.6 ± 25.9	326.7 ± 44.3
Controls	347.8 ± 59.6	335.9 ± 56.9
Omission errors		
Patients	3.6 ± 3.9	4.3 ± 4.9
Controls	0.9 ± 0.9	1.1 ± 1.4
Commission errors		
Patients	20.1 ± 9.2	21.8 ± 10.4
Controls	13.7 ± 7.6	13.6 ± 8.6

Values are mean ± standard deviation.
CPT, Conners' Continuous Performance Test II; Hit RT, reaction time.

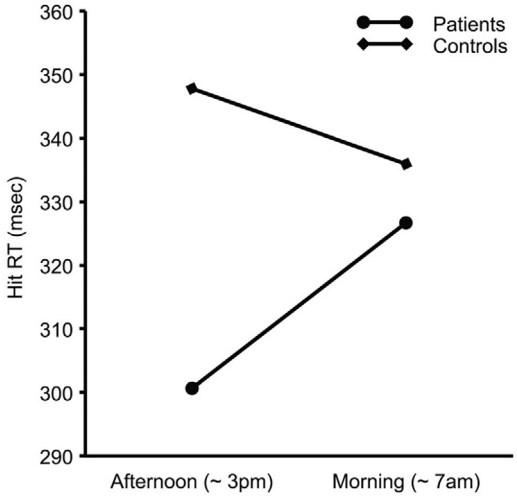

Fig. 1. Conners' Continuous Performance Test II: group (patients, controls) × time (afternoon, morning) interaction for Hit RT [$F(1, 16) = 7.76$, $P = 0.01$]. RT, reaction time.

increase in mean Hit-RT when tested in the morning, relative to that in the afternoon {$F(1, 16) = 7.32$, $P = 0.016$ [95% confidence interval (CI) of difference, 5–46]}. In addition, patients had lower Hit-RT than healthy controls when tested in the afternoon [$F(1, 16) = 4.75$, $P = 0.045$ (95% CI of difference, 1–93)], whereas no statistically significant difference between the groups was found in the morning. Patients generally made more omission errors than controls [main effect $F(1, 16) = 4.69$, $P = 0.046$ (95% CI of difference, 0.06–5.8)]. For commission errors, there were no significant main or interaction effects.

No significant correlations were found within the DSPD group between Hit-RT (afternoon–morning difference) and melatonin increase, diary sleep onset hour, diary sleep length, PSG-TST, SE, and N3. Neither the awakening threshold nor the Hit-RT difference correlated with these variables. Awakening threshold, but not Hit-RT difference, correlated positively with BDI (rho = 0.74, $P = 0.023$).

4. Discussion

Of the nine patients, three could not be awakened from an alarm clock with a sound intensity of 104 dB, whereas all controls either were already awake or woke up from a sound intensity of ≤78 dB. This may point towards a possible dysfunction in sleep/arousal system that may in part explain why some patients seem unable to attend work or school. Awakening threshold did not correlate with either PSG or circadian variables among patients. This suggests that difficult morning awakening may not be a mere reflection of short sleep. A clinical implication is that certain patients may need manual awakening in addition to an alarm clock, at least in the early stages of light treatment before the circadian phase has been shifted.

The trend towards patients being harder to wake up compared to controls was statistically non-significant. This was probably due to a small sample size and large variability within the patient group.

Interestingly, whereas healthy subjects are most likely to wake up from REM sleep [3], all patients who were unable to wake up when exposed to a 104 dB alarm clock sound were in REM sleep. This was contrary to our hypothesis that DSPD awakening problems would be related to slow wave sleep (N3) and suggests a possible REM sleep dysfunction in a subgroup of DSPD patients. This observation seems to be new. To our knowledge, there are no previously reported cases of difficult awakening from REM sleep in the literature.

Current knowledge about REM sleep suggests that 'stimuli incorporation' might be one explanation for the observed difficult awakening. It is not unusual to incorporate external auditory stimuli into a dream [24]. A DSPD subject might then include the sound of an alarm clock into his/her dream, counteracting the expected arousal and awakening. Regrettably, we did not ask patients to recollect dream content in the present study.

The CPT results showed that patients, compared to controls, had increased Hit-RT when tested in the morning as compared to when tested in the afternoon. This supports the hypothesis that the patients' cognitive function is reduced upon awakening. To some extent, this observation may confirm patients' subjective reports of 'sleep drunkenness' when forced to wake up early [17].

No correlation between CPT and PSG or circadian variables was found within the DSPD group. However, reduced TST, reduced SWS, and lower SE may still be contributing factors to the decline in early morning performance when DSPD patients are compared to controls, because the lack of within-group correlation can be explained by a type II error.

DSPD may also affect cognitive function in general, i.e. unrelated to time of day as patients made more omission errors than controls. In addition, patients had faster Hit-RT than healthy controls when tested in the afternoon. These findings suggest that there may be stable trait-like differences between DSPD patients and controls, in addition to the state-dependent change found in relation to Hit-RT.

The high score for depression in our patient group is in agreement with other studies [25,26]. Abe et al. reported that depression is most common in evening chronotypes [26]. Alvarez et al. stated that it is unlikely that depression or personality problems are among the main causes of DSPD [25]. Nevertheless, we observed that high awakening thresholds were associated both with more severe depression and with relatively less REM sleep, suggesting that the possibly interacting effects of depression and sleep structure in DSPD should be investigated further in future studies.

The study has limitations as our sample size was small and the results might not apply to the general DSPD population. A second limitation was that we did not include CPT measurements after a second night with longer sleep durations in patients. Hence, we could not ascertain with our design whether the CPT findings were related to short sleep duration or to DSPD itself. A third limitation was a rather large variability in baseline melatonin recordings. Melatonin was not required for diagnosis, but more stable recordings might improve our ability to detect the effect of the circadian factor on DSPD-related symptoms. We emphasize that our results require independent confirmation and future investigation as there currently is no literature on the subject.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.05.024.

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